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EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	19

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/870,932	Applicant(s) WU ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

1 Applicant's amendment, filed 4/15/03 (Paper No. 16) is acknowledged.
Claims 1-74 have been cancelled previously.
Claims 75-110 are pending and are under consideration in the instant application.

2. Applicant's provision of additional copies of the references previously unavailable to the Examiner is acknowledged with appreciation.

The references have now been considered, as indicated on the attached copy of the PTO-1449 form filed on 10/5/01 (Paper No. 7).

3. This Office Action will be in response to applicant's arguments, filed 4/15/03 (Paper No. 17). The rejections of record can be found in the previous Office Action (Paper No. 14).

Claim Rejections - 35 USC § 112 first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. In claims 83, 85, 95, 97, 107 and 109, it is apparent that the antibody produced by the hybridoma deposited under ATCC Accession No. HB-12366 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification.

It is noted that the specification on page 13 indicates that the 2D9-antibody-producing hybridoma cells were deposited with the ATCC as HB-12366 on 6/6/1997.

In addition, Applicant has assured in Paper No. 16 (filed 4/15/03) that all restrictions will be irrevocably removed upon granting of a patent.

Therefore, the enablement requirement under 35 USC 112, first paragraph is considered to be fulfilled.

6. Claims 75-82, 84-94, 96-106 and 108-110 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies that inhibit binding of the chemokines MIP-1α, MIP-1β, RANTES to human CCR5; does not reasonably provide enablement for antibodies which inhibit binding of other "chemokines" to any "mammalian" CCR5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 4/15/03, have been fully considered but have not been found convincing for the reasons of record in Paper No. 14.

Applicant argues that Table 1 of Zlotnik and Yoshie (Immunity 2000;12:121-127, IDS #AZ4), cited by the Examiner, shows that CCR5 binds the chemokines MIP-1α, MIP-1β, RANTES, as also disclosed in the specification. Applicant argues that there are not an unreasonable number of chemokines that bind CCR5 and concludes that the experimentation required to identify the chemokines that bind CCR5 would not be undue. Applicant also argues that it would not be undue experimentation to provide other mammalian orthologs of human CCR5 and make and use antibodies to these other CCR5 proteins.

However, the Examiner maintains for the reasons set forth in Paper No. 14 that a person of skill in the art is not enabled to make and use an antibody which inhibits binding of *any* "chemokine" to *any* "mammalian" CCR5 as encompassed by the full breadth of the claims as currently recited.

The rejection of record may be found in full in Paper No. 14. For the reasons of record, the disclosure of a single species of CCR5 (human) and three chemokines bound by human CCR5 (i.e., MIP-1α, MIP-1β, and RANTES) does not appear to provide sufficient guidance to direct a person of skill in the art in how to make and use an antibody which inhibits binding of *any* "chemokine" to a CCR5 protein of *any* mammalian origin.

The Examiner acknowledges that Zlotnik and Yoshie teach a new classification system, but their summary of what is known regarding the binding of multiple chemokines to any given receptor underscores that the skilled artisan could not reasonably predict what other newly identified chemokines would also bind human CCR5. In addition, the claims are not limited with respect to human CCR5, but instead encompass any mammalian CCR5. Identification of homologs of human CCR5 is unpredictable for the reasons of record in Paper No. 14.

Thus in view of the extensive breadth of the instant claims, the presence of working examples that are limited to inhibition of binding of the three known chemokine ligands of human CCR5, and the unpredictability associated with identifying other chemokines that bind not only human CCR5, but any mammalian CCR5; the experimentation left to those skilled in the art to make and use the antibodies as currently broadly recited is unnecessarily, and improperly, extensive and undue.

The rejection is maintained for the reasons of record set forth in full in Paper No. 14.

7. Claims 75-82, 84-94, 96-106 and 108-110 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

Applicant's arguments, filed 4/15/03, have been fully considered but have not been found convincing for the reasons of record set forth in full in Paper No. 14.

Applicant argues that an adequate written description has been provided because the claims are limited to those chemokines that bind CCR5, and three examples are described. Applicant also argues that the CC chemokines share a structural motif, implying that the shared motif conveys the function of CCR5 binding.

However, while the Examiner acknowledges that it was well known that the CC chemokine family shared common structure; the shared structure did not convey the function of CCR5 binding since not all CC chemokines bind CCR5. In addition, it is again noted that the instant claims are not limited to antibodies which inhibit binding of chemokines to human CCR5, but instead encompass antibodies that inhibit binding of any chemokine to any mammalian CCR5.

Applicant does not appear to have described what structural attributes make a mammalian protein a "CCR5" protein. Applicant does not appear to have described the common structural attribute that conveys the function of chemokine binding to either human CCR5 in particular or any mammalian CCR5 in general. Absent a sufficient description of the receptor-ligand pairs, there consequently does not appear to be an adequate written description of the instantly recited genus of antibodies that bind any mammalian CCR5 and inhibit binding of the chemokine ligand of that species of CCR5.

Thus the rejection of record set forth in full in Paper No. 14 is maintained.

Applicant is again directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections – 35 U.S.C. §§ 102 and 103

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 75-82, 84-94 and 96-98 stand rejected under 35 U.S.C. 102(e) as being anticipated by Li et al. (US Pat. No. 6,025,154, IDS AE, see entire document) *as evidenced by* Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4).

Applicant's arguments, filed 4/15/03, have been fully considered but have not been found convincing for the reasons of record set forth in full in Paper No. 14.

Applicant argues that Li et al. provide only a generic teaching of antibodies to CCR5/HDGNR10 and do not teach an antibody species that not only binds CCR5/HDGNR10, but also inhibits binding of a chemokine and inhibits one or more functions associated with chemokine binding to the receptor and thus does not teach each and every element of the claim.

Applicant points out that antibodies that bind CCR5 and inhibit chemokine binding do not all necessarily inhibit one or more functions associated with chemokine binding because some antibodies themselves function as agonists and some bind but have no effect on chemokine-induced function. Applicant points to the teachings of Olson et al. (J. Virol. 1999 73(5):4145-4155, IDS # AW5) for support that not all antibodies have the function of inhibiting chemokine binding and one or more functions associated with chemokine binding.

The rejection of record may be found in full in Paper No. 14.

Applicant's comments regarding non-antagonist antibodies (i.e., an antibody that binds but does not inhibit one or more functions associated with chemokine binding) are acknowledged. However, as previously noted, Li et al. explicitly teach assays for screening for *antagonists* of *both* ligand binding and receptor function associated with that binding (see especially columns 11-12).

Applicant's comments regarding the low frequency of antibodies having the instantly recited functional properties among the antibodies of Olson et al. are also acknowledged. However, Olson et al., *unlike* Li et al., did not select for antagonists of chemokine binding. Rather, Olson et al. only selected for antibodies that blocked HIV-mediated envelop fusion and then assayed those antibodies for their effect on chemokine binding.

That agonist antibodies can also be produced is not denied by the Examiner: Li et al. also teach agonist antibodies. However, as discussed fully in Paper No. 14, Li et al. do teach how to make and identify antibodies having the instantly recited functional properties (see especially column 12 at lines 16-21 in view of columns 11-12 and 18).

Thus while the disclosure of genus may not anticipate a species unless some direction is provided to that species; in the instant case the teachings of Li et al. do direct the ordinary artisan to screen for and select those anti-CCR5 antibodies having the instantly recited functional properties of inhibiting binding of a chemokine (i.e., a CCR5 ligand) and inhibiting (i.e., antagonizing) one or more functions associated with binding. Also previously noted, Wu et al. evidence that antibodies that block binding of chemokine ligands to CCR5 bind the second extracellular loop.

The Examiner maintains for the reasons of record in Paper No. 14 that the reference teachings anticipate the instant claimed invention. The rejection is maintained.

10. Claims 75-82, 84-94 and 96-98 stand rejected under 35 U.S.C. 102(e) as being anticipated by Hoxie (US Pat No. 5,994,515, IDS AB, see entire document) *as evidenced by* Olson et al. (J. Virol. 1999; 73:4145-4155, IDS #AW5) and Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4).

Applicant's arguments, filed 4/15/03, have been fully considered but have not been found convincing for the reasons of record set forth in full in Paper No. 14.

Applicant argues that the antibodies taught by Hoxie do not necessarily possess the instantly recited functional properties. Applicant points to Atchison et al. (Science 1996; 274:1924-926, IDS # AZ5) and Gosling et al., (PNAS 1997 94:5061-5066, IDS #AX5) for evidence that HIV viral co-receptor activity is dissociable from chemokine ligand-dependent signaling of CCR5.

The rejection of record may be found in full in Paper No. 14.

The Examiner acknowledges that HIV co-receptor functions and functions associated with chemokine binding to CCR5 can be dissociated, as also taught by Wu et al. (see entire document). However, the Examiner has previously cited Olson et al. to show that the antibodies *most effective* at inhibiting HIV membrane fusion and viral entry (assays of HIV infection) *are the antibodies that also inhibit calcium flux* (i.e., a function associated with binding of a chemokine to CCR5) in response to the chemokine RANTES binding to CCR5 (see especially Table 1 and the comments with respect to PA14 and 2D7 on pages 4147-4150).

Thus the Examiner maintains that the screen taught in Hoxie that assayed for inhibition of HIV infection (i.e., cell fusion and viral entry) would *necessarily* result in antibodies that inhibited chemokine binding and one or more functions associated with chemokine binding to CCR5. Not only were such monoclonal antibodies produced upon immunization with CCR5, but because Hoxie teaches that the antibodies should be selected for inhibition of HIV infection, the ordinary artisan would clearly have selected for those monoclonal antibodies which also inhibited chemokine binding to CCR5 because *those were the antibodies most effective at inhibiting HIV infection.*

The Examiner maintains for the reasons of record in Paper No. 14 that the reference teachings anticipate the instant claimed invention. The rejection is maintained.

11. Claims 75-82, 84-94, 96-106 and 108-110 stand rejected under 35 U.S.C. 102(e) as being anticipated by Littman et al. (US Pat. No. 5,939,320, IDS # AA, see entire document) *as evidenced by* Olson et al. (J. Virol. 1999; 73:4145-4155, IDS #AW5) and Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4).

Applicant's arguments, filed 4/15/03, have been fully considered but have not been found convincing for the reasons of record set forth in full in Paper No. 14.

Applicant argues that the antibodies taught by Littman et al. do not necessarily possess the instantly recited functional properties for the reasons set forth supra with respect to the teachings of Hoxie.

The rejection of record may be found in full in Paper No. 14.

Applicant's arguments with respect to the inherency of the instantly recited functions in antibodies selected for inhibition of HIV infection and that there is no requirement that such antibodies actually be produced have been discussed supra with respect to Hoxie. To summarize those arguments, while the data do show that HIV co-factor functions and functions associated with chemokine binding are dissociable, that two functions may be dissociated does not indicate that an antibody that inhibits HIV would not inherently block binding of chemokines to CCR5.

Antibodies which inhibit chemokine binding and functions associated with chemokine binding have been found to be those that are most efficient at inhibiting CCR5 co-receptor activity. Thus the Examiner maintains that a screen such as taught in Littman et al. that assayed for inhibition of HIV infection would *necessarily* include antibodies that inhibited chemokine binding and one or more functions associated with chemokine binding to CCR5 because *those were the antibodies most effective at inhibiting HIV infection.*

The Examiner maintains for the reasons of record in Paper No. 14 that the reference teachings anticipate the instant claimed invention. The rejection is maintained.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chuntharapai et al. (US Pat. No. 5,543,503, IDS AD) in view of *either* Raport et al. (J. Biol. Chem. 271:17161-17166 1996, IDS # AW), Samson et al. (Biochem. 35:3362-3367 1996, IDS #AV), *or* Combadiere et al. (J. Leukoc. Biol. 60:147-152 1996, IDS #AT3), *as evidenced by* Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4).

Applicant's arguments, filed 4/15/03, have been fully considered but have not been found convincing for the reasons of record set forth in full in Paper No. 14.

The rejection of record may be found in full in Paper No. 14. Applicant's individual points are addressed below.

With respect to Chuntharapai et al., Applicant asserts that Chuntharapai et al. does not teach or suggest that antibodies may inhibit a function associated with binding of a chemokine (IL-8) to its receptor (IL-8R). Applicant asserts that Chuntharapai et al. only teach to select for antibodies that inhibit binding of a chemokine to its receptor, not for those that further inhibit a function associated with that binding. Applicant also argues that Chuntharapai et al. could not have screened for inhibition of functions associated with binding of IL-8 to the IL-8R because there were no good assays.

Chuntharapai et al. distinguish between antagonist antibodies, agonist antibodies, and those which bind but do not block chemokine binding and receptor activation (see e.g., column 30, especially lines 7-10). Contrary to Applicant's assertions, Chuntharapai et al. do teach that antagonist antibodies can also be screened for their ability to block activation of IL-8R-expressing cells (e.g. column 30, especially lines 20-31 and also see "Summary of the Invention, especially lines 33-41). One of ordinary skill in the art, would have certainly understood that these statements by Chuntharapai et al. indicated that not only was inhibition of chemokine binding by the antibody desirable (and a property of the antibody which for which a screen existed); but also inhibition of the functions normally associated with binding of the chemokine to its receptor. In addition, Chuntharapai et al. also teach that it is such antagonist antibodies that are therapeutic candidates (see e.g. column 30 at lines 21-31). Finally, it is noted that many assays for inhibition of a function associated with the binding of the chemokine IL-8 were well known in the art at the time of Chuntharapai's teachings, as reviewed in the "Background of the Invention" at columns 1-2.

Applicant again points to the teachings of Olson et al. (J. Virol. 1999; 73:4145-4155, IDS #AW5) as evidence that antibodies which bind CCR5 and inhibit binding of a chemokine ligand may themselves trigger receptor function.

The Examiner notes that although Olson et al. (like Chuntharapai et al.) do comment on page 4147, 2nd column at lines 46-48 that antibodies may be antagonists, agonists, or have no effect on receptor-mediated intracellular signaling (a requisite event in initiation of receptor-based function); they note that agonists antibodies (i.e., those that bind and stimulate receptor function) are rare. More importantly, Olson et al. go on to show that none of the antibodies to CCR5 that they test are agonists (see especially full bridging paragraph of page 4147-4148). It is further noted that although most of the antibodies of Olson et al. do not inhibit calcium flux in the presence of the CCR5 ligand RANTES (i.e., they are not antagonists); these antibodies were selected on the basis of inhibiting HIV binding, which as Applicant has noted is a function dissociable from chemokine binding. Thus the antibodies of Olson et al. are not indicative of the ability of antibodies selected on the basis of inhibition of chemokine binding to also inhibit a function associated with chemokine binding.

Applicant also points to a copy of the Newman 1.132 Declaration (originally filed 3/1/99 in parent USSN 08/893,911), and to Frade et al. (J. Immunol. 1997; 159:5576-5584, IDS# AY5) for evidence that not all antibodies that bind a receptor and inhibit ligand binding also inhibit a function associated with binding of the ligand to the receptor.

As acknowledged supra, clearly it was well known in the art that both agonist and antagonist (as well as antibodies lacking functional effects) could be generated to receptor proteins. However, the prior art also recognized that antagonist antibodies could be screened for and selected, and that such antagonist antibodies were desirable (see the comments with respect to the teachings of Chuntharapai et al. supra).

Applicant has further argued that it is unpredictable what effect, if any, an antibody will have on functions associated with binding of the chemokine to its receptor given only a teaching that binding of the chemokine is inhibited.

However, the Examiner notes that it was well known in the art at the time the invention was made that most antibodies that inhibited binding of a ligand to its receptor were antagonist antibodies (i.e., also inhibited the functions associated with binding of the ligand to the receptor). In addition, even were agonist antibodies common among those antibodies produced to a chemokine receptor such as CCR5 (as noted supra, they were not); it is still predictable what effect an antibody that binds a chemokine receptor and blocks ligand binding will have *because the art teaches screening for an antagonist antibody*, as do the references discussed supra and previously.

Applicant has also argued that there is no reasonable expectation of success in obtaining anti-CCR5 antibodies that inhibited binding of a chemokine ligand to CCR5 and inhibited one or more functions associated with binding of the chemokine to CCR5.

For further support for this argument, Applicant asserts that CCR5 is not equivalent to an IL-8 receptor since they have distinct amino acid sequences and structures, and points to the Newman 1.132 Declaration originally filed 3/1/99 in parent USSN 08/893,911 for support that antibodies to CCR5 were difficult to produce. Applicant also again points to Olson et al. (discussed supra) that only one antibody of the panel produced by Olson et al. inhibited the calcium flux associated with binding of a chemokine ligand to CCR5.

As noted supra, although most of the antibodies of Olson et al. do not inhibit calcium flux in the presence of the CCR5 ligand RANTES (i.e., they are not antagonists, ibid); these antibodies were selected on the basis of inhibiting HIV-mediated cell fusion. Thus the antibodies of Olson et al. are not indicative of the ability of antibodies selected on the basis of inhibition of chemokine binding alone, and certainly are not indicative of antibodies selected to antagonize CCR5 function. However, it must also be noted that Olson et al. were able to produce several antibodies to CCR5 that had the function they desired and screened for (inhibition of HIV-mediated fusion).

With respect to the Newman Declaration, it was well established in the field of antibody production and of general knowledge to one of ordinary skill in the art at the time the invention was made that given the proper immunization strategy and screening method, there was a reasonable expectation of producing an antibody having the desired specificity and functional property. The amount of screening involved in isolating the desired antibody did not indicate that there is not a reasonable expectation of success, as extensive screening was a matter of routine experimentation in the art. It is noted that methodology employed by Applicant to reduce to practice an antibody with the recited properties did not differ unobviously from that taught by the instant references.

The Newman Declaration under 37 CFR 1.132 filed 4/15/03 is therefore insufficient to overcome the rejection of record as set forth in the last Office action.

The Examiner maintains for the reasons of record in Paper No. 14 that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is therefore maintained.

14. Claims 80-82, 86, 92-94, 98, 104-106 and 110 stand rejected under 35 U.S.C. 103(a) as being unpatentable over

Chuntharapai et al. (US Pat. No. 5,543,503, IDS AD) in view of *either* Raport et al. (J. Biol. Chem. 271:17161-17166 1996, IDS # AW), Samson et al. (Biochem. 35:3362-3367 1996, IDS #AV), *or* Combadiere et al. (J. Leukoc. Biol. 60:147-152 1996, IDS #AT3), *as evidenced by* Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4),

as applied to claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 above;
and further in view of Ramakrishnan et al. (US Pat. No. 5,817,310, of record, see entire document).

Applicant's arguments, filed 4/15/03, have been fully considered but have not been found convincing for the reasons of record set forth in full in Paper No. 14.

The rejection of record may be found in full in Paper No. 14.

Applicant argues that Ramakrishnan et al. do not remedy the defects of Chuntharapai et al. in view of either Raport et al., Samson et al or Combadiere et al. as evidenced by Wu et al.

The rejection in full may be found in Paper No. 14.

Applicant's comments regarding Chuntharapai et al. in view of any of Raport et al., Samson et al. and Combadiere et al. et al. have been discussed supra and have not been found convincing.

The Examiner therefore maintains for the reasons of record in Paper No. 14 that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is therefore maintained.

Double Patenting

15. Applicant's statement in the Remarks field 4/15/03 that a terminal disclaimer with respect to claims 1-36 of USSN 08/893,911 will be filed upon the identification of allowable subject matter in the instant application is acknowledged.

The obviousness-type double patenting rejection of the instant claims is therefore held in abeyance.

Conclusion

16. No claim is allowed.

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
June 21, 2003

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
6/23/03